NCRP

Second Cancers Following Radiotherapy for Cancer

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Introduction

The study of second cancer risk after radiotherapy provides a unique opportunity to study carcinogenesis since large groups of humans are deliberately exposed to substantial doses of radiation in order to cure disease. Detailed radiotherapy records for cancer patients allow precise quantification of organ dose, and population-based cancer registries are frequently available to provide access to large groups of patients who are closely followed for long periods. Moreover, cancer patients treated with surgery alone (no radiation) are frequently available to serve as a non-irradiated comparison group. New information can be provided on relatively insensitive organs, and low dose exposures in the range of scientific interest are received by organs outside the radiation treatment fields. This paper will review several recently completed studies that characterize the risk of radiation-induced second cancers. Emphasis will be given to studies providing new information on the dose-response relationship of radiation-induced leukemia, breast cancer and lung cancer.

Second Leukemia after Radiotherapy

Although several studies have evaluated the risk of leukemia following high-dose radiotherapy for cancer, few investigations have quantified the relationship between leukemia risk and dose and the modifying effects of radiation quality, age at first exposure, and time since irradiation (UNSCEAR, 1994). Moreover, the combined effect of radiotherapy and chemotherapy on leukemia risk has not been well explored.

Leukemia Risk after Uterine Corpus Cancer

To provide additional information on these issues, a large international study was undertaken of risk of leukemia following pelvic radiotherapy for uterine corpus cancer (UCC) (Curtis *et al.*, 1994). The design of the study was patterned after a large study of cervical cancer patients (Boice *et al.*, 1987; Stovall *et al.*, 1989). A nested case-control study was conducted within a cohort of 110,000 patients from 9 population-based cancer registries in the United States, Canada and Europe. Despite substantial radiation exposure to the bone marrow, the relative risk (RR) of all leukemia excluding chronic lymphocytic leukemia following radiotherapy was only modestly increased, 1.9 (95% confidence interval (CI) = 1.3-2.9), based on 160 leukemia cases and 622 matched controls. This is the first study to evaluate leukemia risk among a mostly elderly population; the average age at exposure was 62 years. Risk did not vary by age when first irradiated and increased risks were demonstrated for those irradiated at ages over 65 years (RR = 1.8, CI = 0.9-3.5). No increase in risk was found for chronic lymphocytic leukemia (54 cases, RR = 0.90, CI = 0.4-1.9), one of the few malignancies never linked to radiation exposure.

An important feature of the UCC study was the large number of patients treated with surgery alone (38%), thus providing an excellent comparison group that minimizes potential biases due to selection and the underlying disease. Also this study was unique in being able to compare two very different types of radiation exposures: 29% of patients received external beam therapy which was fractionated and spread over 4–6 weeks. A high dose rate was used and the total dose averaged over the active bone marrow was high (mean, 9.9 Gy). In contrast, brachytherapy patients received continuous exposures over a much shorter period (2-3 days), resulting in much lower dose rates and lower average total marrow doses (mean, 1.7 Gy).

The risk following brachytherapy was found to be similar to that after external beam therapy (RR = 1.8 versus 2.3, respectively). However, because of the large difference in mean marrow dose there was about a 4-fold difference in the crude excess risk per Gy (excess relative risk = relative risk - 1), 0.47 versus 0.13, indicating that external beam therapy was much less leukemogenic than brachytherapy, per unit dose.

For each individual, radiation physicists estimated the dose to 17 bone marrow components using mathematical models, water and anthropomorphic phantoms. Marrow in the pelvis received very high doses, about 5 Gy for brachytherapy and 18-43 Gy for external beam therapy. In contrast,

marrow in the sternum and thoracic spine received doses of less than 1 Gy. The mean dose was weighted by the percent of active marrow in each component and summed to give the total mean weighted marrow dose. The precision of the dose estimates for partial body marrow exposures was restricted by several factors. First, there is the inhomogeneous dose distribution, with extensive cell killing in areas of high dose exposure. Second, the dose estimation does not account for possible movement throughout the circulatory system of the stem cells, the presumed target cells of leukemogenesis. Finally, there is the protracted nature of the exposures which allows time for cellular repair of radiation damage.

Overall, leukemia risk was significantly increased at about a 2 to 3-fold level across a wide dose range. Model fitting found the pattern most consistent with a flat dose-response relation. In the lower dose range, where most exposure was from brachytherapy, the risk estimates appear to be lower than would be predicted from studies of the atomic bomb survivors (NAS/NRC, 1990; Preston *et al.*, 1994). A significant linear trend was observed up to mean doses of 1.5 Gy (test of trend, $P=0.03$) after which risk appeared to drop off. One explanation for differences with the A-bomb series may be that continuous low dose exposures given at low dose rates are less leukemogenic than the whole body nearly instantaneous doses received by the atomic bomb survivors. Alternatively, partial-body exposures may be different in effect than whole body exposures. At higher doses delivered by external beam therapy, there was a tendency for risk to rise with increasing dose, however, much of the upward trend in risk at the highest doses appeared to be due to a small subgroup of women with a particularly high risk. In contrast to the other patients, these women received substantial doses to the central trunk of the body as well as the pelvis. A flat dose response was seen when these women were excluded. These results are in general agreement with the cervical cancer study (Boice *et al.*, 1987) in which most women received combined external beam therapy and brachytherapy (RR = 1.88, 90% CI = 0.9-3.9). In the cervical cancer study, risk appeared to decline or taper off at high doses, although numbers of cases in this range were small.

Leukemia Risk Following Breast Cancer

Leukemia following breast cancer was studied in a large cohort of 82,000 women from 5 areas in the United States who were treated during the 1970's and early 1980's (Curtis *et al.*, 1992). This study was able to address an important question of whether radiotherapy potentiates the effect of chemotherapy. Included in the study were 90 leukemia cases and 264

matched controls. Radiotherapy during this period usually consisted of high-dose fractionated external beam therapy to the chest wall and regional lymph nodes after mastectomy. The mean dose averaged over the total active bone marrow was 7.5 Gy.

Patients treated with radiotherapy, and no chemotherapy, were found to have a significantly increased 2.4-fold risk (95% CI = 1.0-5.8) of acute nonlymphocytic leukemia or myelodysplastic syndrome in comparison to breast cancer patients treated with surgery alone (no radiotherapy and no chemotherapy). A 10-fold risk was found for patients treated with alkylating agents but not radiotherapy, with a much higher risk found for melphalan than for cyclophosphamide. Risk was particularly high for women receiving both radiotherapy and alkylating agents (RR = 17, CI = 6.4-47.0)). Important findings from this study were that high-dose radiotherapy added significantly to the risk of leukemia after chemotherapy, in an analysis that accounted for radiation dose and amount of alkylating agents received, and that the relationship appeared consistent with a multiplicative model.

A surprisingly strong increase in risk with increasing dose was seen among patients treated with radiation (test of trend, $P<0.001$). A 7-fold risk was associated with average bone marrow doses of more than 9 Gy (CI = 2.0-24.9), after adjusting for the effects of alkylating agent therapy. The risk was equally as high for this high-dose group when the analysis was restricted to those treated with radiation alone (RR = 10.4).

No evidence of an increased risk of leukemia was found in a smaller study of breast cancer patients treated in Connecticut prior to the widespread use of adjuvant chemotherapy (1935-1972) (Curtis *et al.*, 1989). However, these earlier treatments used orthovoltage machines and delivered doses to the bone marrow that were about 25% lower than in the larger study cited above.

Treatment practices have changed since these studies and currently the majority of women are treated with localized radiation to the breast after conservative surgery, a therapy that delivers substantially lower doses to the total bone marrow. An evaluation of the leukemia risk associated with these newer therapies is needed in the future, especially since radiation is now widely used for early stage disease.

Leukemia Summary

In reviewing the results for leukemia risk after partial body radiotherapy, one is struck by the remarkable consistency of about a 2-fold relative risk across a wide dose range for most studies (Curtis *et al.*, 1992; 1994;

Boice *et al.*, 1987; Inskip *et al.*, 1993; Kaldor *et al.*, 1990). In the lower dose range where mostly brachytherapy was used and cell killing is a lesser factor, leukemia risks are substantially lower than estimates derived from studies of the atomic bomb survivors. This could be attributed partially to inaccuracies in dosimetry but may be explained by the low dose rates for brachytherapy. In the higher-dose range where most patients were treated with external beam therapy, it is clear that the risks are far below that projected from standard risk estimates, where several hundred leukemias would be expected based on the doses received. Clearly the relationship of leukemia risk to radiation dose is complex, and reflects the interplay of several competing processes. There is likely substantial destruction of a large proportion of the marrow cells exposed to high doses, whereas marrow cells exposed to lower doses would have the potential for malignant transformation. In addition, the external beam therapy is protracted over several weeks allowing sufficient time for cellular repair.

Second Primary Solid Cancers after Radiotherapy

Most evidence on the relation between radiation dose and risk of second primary solid tumors following cancer radiotherapy comes from the International Cervical Cancer Study (Boice *et al.*, 1988; 1989) and studies of childhood cancer (Tucker *et al.*, 1987; 1991; de Vathaire, 1988). Recently, several investigations of cancer patients have quantified the risk of radiation-induced second cancers of the breast and lung.

Radiation-induced Second Breast Cancer

Multiple epidemiologic studies have evaluated the risk of contralateral breast cancer due to radiotherapy for an initial breast cancer. Although most investigations found no association between radiotherapy and second breast cancer risk, the studies may have been too small to detect a significant risk among the most susceptible subgroup—young women who survived more than 10 years. Two studies calculated dose to the contralateral breast, and had sufficient numbers to evaluate risk by age and time after radiation.

Boice *et al.* (1992) conducted a case-control study including all patients in the state of Connecticut diagnosed from 1935 to 1982, who survived 5 or more years after their breast cancer diagnosis. In a parallel study, Storm and co-workers evaluated 8-yr breast cancer survivors initially diagnosed between 1943 and 1978 in Denmark (Storm *et al.*, 1992). Both studies

were large with over 500 cases of second cancers in the contralateral breast. In the Connecticut study only 21% were treated with radiotherapy, whereas in Denmark most women were irradiated. The mean dose averaged over the entire breast was about 2.5-2.8 Gy, with much higher doses to the medial portion of the breast.

The results from both studies show that radiotherapy for breast cancer contributed little to the risk of second cancer in the opposite breast. In the Connecticut series, women that were irradiated had a non-significant 19% increase in risk in comparison to non-irradiated women. There was little evidence of excess breast cancers in Denmark. Radiation-induced breast cancer has been shown to have a latent period generally in excess of 10 years, and so it is of interest that there was a small but marginally significant elevation in risk among 10 + year survivors in Connecticut (RR = 1.33, 95% CI = 0.99 - 1.78). In Denmark, there was no evidence that risk varied by time since therapy.

It is also well known that age at irradiation is an extremely important determinant of radiation-induced breast cancer risk (UNSCEAR, 1994). Radiation risk declines with increasing age and low risks are seen for those exposed over the age of 40 years. In agreement with these studies, there was no indication of an excess risk of contralateral breast cancer among women irradiated at ages over 45 years in either the Connecticut or Danish series. However, younger women treated with radiotherapy in Connecticut had a small but significant 59% increase in the risk of second breast cancer in comparison to younger patients treated with surgery alone. No corresponding increase was seen in the Danish study.

Both the Connecticut and Danish studies agree that there is no evidence that breast cancer risk is related to radiation dose for women irradiated over the age of 45 years. However, a significant trend of increasing risk with increasing dose was seen among Connecticut patients irradiated at younger ages (ages < 45 years, linear trend $P = 0.03$). At mean doses over 2 Gy there appeared to be a leveling off in risk. For the younger age group, the estimated relative risk at 1 Gy (RR = 1.21, ages < 45 years) was comparable to risk levels among patients with tuberculosis treated with fluoroscopy in the United States (Boice *et al.*, 1991). Thus while these women have a high risk of a second breast cancer, their risk of radiation-induced breast cancer is quite similar to the risk among women without breast cancer. The authors concluded that, overall, the absolute number of excess contralateral breast cancers due to radiation was small and unlikely to be a major factor in treatment decisions.

Second cancers following treatment for Hodgkin's disease are an important clinical concern with an estimated 20% of patients expected to have a second cancer after 20 years of follow-up (van Leeuwen *et al.*, 1994). Recent studies have highlighted a high increase in breast cancer risk among young girls treated with mantle irradiation (Hancock *et al.*, 1993; Bhatia *et al.*, 1996; Travis *et al.*, 1996a).

Hancock and coworkers (1993) found an overall 4-fold risk of secondary breast cancer following Hodgkin's disease, but excess cancers were limited to young women exposed before the age of 30 years. The relative risk for those irradiated at ages before 15 years was exceptionally high, 136-fold (95% CI = 34-371). The Late Effects Study group recently confirmed these findings among children with Hodgkin's disease (Bhatia *et al.*, 1996). Both studies documented a greatly increased risk of breast cancer among long-term survivors, although, in the 1996 study, incomplete follow-up among healthy patients surviving beyond 15 years may have overestimated this risk somewhat (Donaldson and Hancock, 1996). The large breast cancer excess was thought to be related to the high radiation dose to the mantle field (40-45 Gy) used with past radiotherapy, the young age at exposure, and possibly to the immune dysfunction experienced by Hodgkin's disease patients (Boice, 1993). Lower dose radiation (15-25 Gy) is currently employed among children with Hodgkin's disease in an attempt to minimize these late effects, as well as lead blocks used to minimize exposure to healthy tissue.

Lung Cancer Risk and Radiation Dose

Several recent studies have reported that long-term survivors of breast cancer have about a 2-fold risk of lung cancer after radiotherapy (Inskip and Boice, 1994; Inskip *et al.*, 1994; Neugut *et al.*, 1993; 1994; Travis *et al.*, 1995b). Each of these studies evaluated patients treated with past radiotherapy techniques which delivered high doses to the lungs.

In parallel with the previously discussed contralateral breast cancer study in Connecticut (Boice *et al.*, 1992), Inskip and coworkers (1994b) conducted a small case-control study of 61 breast cancer patients who developed lung cancer 10 or more years after treatment and 120 matched controls; 17 lung cancer cases received radiotherapy as treatment for their breast cancer. Despite very high doses to the lung the risk of subsequent lung cancers was low (RR = 1.8, 95% CI = 0.8-3.8) and not significantly increased. The analysis by Neugut and colleagues (1994) suggested that among smokers, the absolute risk of radiation-induced lung cancer is

much greater than among nonsmokers. However, smoking histories were incomplete, and the issue needs further study (Inskip, 1994a).

In the Inskip study (1994b) the mean dose to the ipsilateral lung was estimated to be about 15 Gy and to the contralateral lung was 5 Gy. There was a tendency for risk to increase with increasing dose to the affected or cancerous lung up to about a mean dose of 7 Gy; thereafter risk leveled off. The relation of risk with dose was not significant (test of trend, $P = 0.18$). The best estimate of the excess RR was 0.20 excess cancers per Gy to the affected lung, substantially below estimates from the A-bomb series. Differences could be due to the protracted exposures or to inadequacies in dose estimation. Dose was averaged across the whole cancerous lung which does not account for the fact that parts of the lung receive very high, possibly cell killing doses. Ideally one would want to estimate dose to the point of tumor, but identifying the origin of the tumor can be difficult with widespread lung cancer. Further study is needed to quantify the interaction of radiation with smoking and to evaluate risk associated with the lower dose breast radiotherapy in current use.

Hodgkin's disease patients have a high risk of secondary lung cancer that occurs early in the follow-up period (Boivin *et al.*, 1995; Swerdlow *et al.*, 1992; Travis *et al.*, 1995a; Tucker *et al.*, 1988, van Leeuwen *et al.*, 1995; Kaldor *et al.*, 1992). Two nested case-control studies have explored the relationship of risk and lung dose. The study by van Leeuwen and colleagues (1995) in the Netherlands was small, with 30 lung cancer cases and 82 matched controls, but had two important strengths: dose was estimated to the lung lobe or bronchi where the lung cancer occurred and data was obtained on pack-years of smoking. A significant elevation in risk with increasing mean lung dose was found (test of trend, $P = 0.01$). High risks of over 7 fold were associated with lung radiation doses over 5 Gy as compared with patients receiving doses less than 1 Gy. No link between lung cancer risk and chemotherapy was found. The study by Kaldor *et al.* (1992) was larger (98 cases, 259 matched controls) but lung dose estimates and data on smoking history were less precise. Radiation dose was averaged across the entire lung and information on smoking duration was not available. Kaldor and colleagues found only a slight non-significant increase in risk with increasing radiation dose for patients who did not receive chemotherapy ($RR = 1.6$ for doses >2.5 Gy compared with <1 Gy, test of trend, $P = 0.48$). A significant 2-fold elevated risk was seen among patients receiving chemotherapy but no radiotherapy in comparison to patients treated with radiotherapy alone.

The Netherlands study examined the modifying effect of smoking on the radiation dose-response relationship of lung cancer. Overall, the total amount ever smoked was related to lung cancer risk, but the trend was not significant ($P = 0.13$) and the strongest relation was the number of pack-years smoked after Hodgkin's disease diagnosis. A significant increase in lung cancer risk over categories of radiation dose was observed among subjects who smoked more than 1 pack-years after diagnosis (test of trend, $P = 0.01$). There was no evidence for a trend with radiation dose for those smoking less than 1 pack-year ($P = 0.43$). Although this study needs to be confirmed with larger numbers, it was important in suggesting that radiation may interact multiplicatively with smoking and that patients who continue to smoke after radiotherapy may be at especially high risk.

Second Solid Cancers Linked Only to High Radiation Doses

Several other second cancers have been linked *only* to radiation when given at very high doses. No radiation-association has been reported for these sites in the atomic bomb survivor studies (Thompson *et al.*, 1994). Excesses of rectal cancer have been found after high-dose pelvic radiotherapy (mean dose 30-60 Gy) with a strong dose-response demonstrated in the cervical cancer study (test of trend, $P = 0.002$) (Boice *et al.*, 1988). Elevations of rectal cancer have also been observed in cohorts of irradiated ovarian and endometrial cancer patients, although dose estimation was not performed (Curtis *et al.*, 1985; Travis *et al.*, 1996).

Several studies have linked high-dose radiation (>10 Gy) to the risk of a second cancer of the bone, and among children dose was significantly related to radiation dose (Hawkins *et al.*, 1996; Tucker *et al.*, 1987). Patients with hereditary retinoblastoma, a rare cancer of the eye, have an exceptionally high risk of developing osteosarcoma and connective tissue cancers (Eng *et al.*, 1993), which has been related to a mutation of the retinoblastoma gene. Recent studies have found that radiation heightens this already elevated risk, among retinoblastoma patients who have the genetically linked disease.

Second cancer of the uterine corpus has been related to extremely high dose radiation among cervical cancer patients (mean dose, 165 Gy). This study also detected a significant dose-response relation for vaginal cancer (mean dose, 66 Gy; test of trend, $P = 0.02$).

Current and Future Studies

Two new studies are evaluating leukemia risk after cisplatin therapy for cancer of the ovary and testis, and the interaction of this drug with radiation. A new study of Hodgkin's disease patients will evaluate the risk of second cancers of the lung and breast with respect to radiation dose. Hodgkin's disease patients are young when exposed to radiation and thus their lifetime risk of cancer could be exceptionally high. Retinoblastoma studies will continue to focus on second cancer risk among a population of genetically susceptible individuals. Finally a study is underway of over 20,000 bone marrow transplant recipients. This treatment has increased dramatically over the last decade and a projected 30,000 bone marrow transplants will be performed in 1996 worldwide. Patients have unique exposures: *whole body* irradiation at doses of 10-15 Gy, intensive chemotherapy, and severe immune suppression.

Conclusion

As survival for cancer patients continues to improve, more of these patients will be at risk to develop a new malignant neoplasm as a result of their curative treatment. Thus, studies of irradiated cancer populations will continue to offer unique opportunities for epidemiologic research to address questions of radiation carcinogenesis that are of clinical and public health relevance.

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Discussion

Sarah Donaldson from Stanford:

As a collaborator in the Stanford Hodgkin's disease late effects studies, I would like to add some perspective on the late effects in Hodgkin's disease survivors and, in fact, any cancer survivor. Stanford originally reported a high incidence of breast cancer in Hodgkin's disease survivors, where the effect of age at time of treatment was much more dramatic in terms of relative rather than absolute excess risks in part because of the rarity of breast cancer among young women (Hancock *et al.*, 1993). Also important was the effect of length of follow up; bad news travels fast and when patients develop a serious condition like a second cancer, they come back to medical attention immediately for treatment. When patients are cured of their cancer, they coast along and may not return for follow up. Often this leads to a difference in follow-up between the patients who develop a second cancer and those who do not. It is also important to realize that current treatment today is not the same as those operational in the 1960's when Hodgkin's disease patients were first being cured with radiotherapy. We no longer use the same high doses nor do we irradiate the same large volumes of tissue; and when chemotherapy is administered,

alkylating agents are no longer used. So there is promise that patients treated today will not experience the same high incidences of second cancer that have been reported. Finally, and perhaps most important, is to understand the seriousness of the underlining disease being treated. If we didn't use effective agents such as radiation, which is the single most effective agent in the treatment of Hodgkin's disease, we wouldn't be curing our patients. Ironically, the hallmark of effective curative therapies used in the past, appears not only to be prolonged survival but also an associated risk of second cancers.

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Rochelle Curtis:

Those are excellent points which I understand are more fully described in your recent editorial in the New England Journal of Medicine, discussing the risk of breast cancer following Hodgkin's disease (Bhatia *et al.*, 1996; Donaldson and Hancock, 1996). The editorial describes potential biases associated with unequal follow up among patients who do and do not develop a second cancer. Because the number of long-term survivors is small, any bias associated with differential follow-up would result in an overestimation of the actual risk involved. Such discussion points to the need for both complete follow-up of patients treated in years past and for continued studies to evaluate the possible risks associated with new (but potentially less toxic) curative therapies.

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